UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte
TRACY D. WILKINS, DAVID M. LYERLY, J. SCOTT MONCRIEF, DANKA PAVLIAKOVA, RACHEL SCHNEERSON, and JOHN B. ROBBINS

Appeal No. 2007-3219
Application No. 09/545,772
Technology Center 1600

Decided: October 17, 2007

Before DEMETRA J. MILLS, ERIC GRIMES, and LORA M. GREEN, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

The Appellants appeal the Examiner's final rejection of the claims for obviousness.

We have jurisdiction under 35 U.S.C. § 6(b) (2006).

Representative claims read as follow:

1. An immunogenic composition for eliciting an immune response to a pathogenic organism which composition comprises a recombinant protein conjugated to a polysaccharide component, wherein said protein comprises the toxin A repeating units (rARU) of *Clostridium difficile* and said polysaccharide component is an antigen of a pathogenic microorganism, which pathogenic microorganism is other than *C. difficile*, wherein said composition is formulated for injection.

20. The immunogenic composition of claim 1, wherein said pathogenic microorganism is selected from the group consisting of: *Streptococcus pneumoniae; Neisseria meningitidis; Escherichia coli;* and *Shigella.*

Cited References

Thomas, Jr. US 5,919,463 Jul. 6, 1999

Ali Fattom et al., "Synthesis and Immunologic Properties in Mice of Vaccines Composed of *Staphylococcus aureus* Type 5 and Type 8 Capsular Polysaccharides Conjugated to *Pseudomonas aeruginosa* Exotoxin A," 58(7) *Infection and Immunity*, 2367-2374 (1990) (hereinafter "Fattom").

Sarvamangala J.N. Devi et al., "Antibodies to poly [(2→8)-α-*N*-acetylneuraminic acid] and poly [(2→9) – α – *N* – acetylneuraminic acid] are elicited by immunization of mice with *Escherichia coli* K92 conjugates: Potential vaccines for groups B and C meningococci and *E. coli* K1," 88 *Proc. Natl. Acad. Sci.* USA, 7175-7179 (1991) (hereinafter "Devi").

Rachel Schneerson et al., "Synthesis of a Conjugate Vaccine Composed of Pneumococcus Type 14 Capsular Polysaccharide Bound to Pertussis Toxin," 60(9) *Infection and Immunity*, 3528-3532 (1992) (hereinafter "Schneerson").

David N. Taylor et al., "Synthesis, Characterization, and Clinical Evaluation of Conjugate Vaccines Composed of the O-Specific Polysaccharides of *Shigella dysenteriae* Type 1, *Shigella Flexneri* Type 2a, and *Shigella sonnei* (*Plesiomonas shigelloides*) Bound to Bacterial Toxoids," 61(9) *Infection And Immunity*, 3678-3687 (1993) (hereinafter "Taylor").

Claim Grouping

We select claim 1 as representative of each of the rejections before us as Appellants have not provided separate argument for individual claims in the Brief. 37 C.F.R. 41.37(c)(1)(vii) (2006).

Grounds of Rejection

Claims 1, 3, 6, 13-15, 19, 20, 23, 24 and 36-39 stand rejected under 35 U.S.C. § 103(a), for obviousness over Thomas in view of Schneerson.

Claims 1, 3, 6, 13-15, 19, 20, 25, 26 and 36-39 stand rejected under 35 U.S.C. § 103(a), for obviousness over Thomas in view of Taylor.

Claims 1, 3, 6, 13-15, 19, 20, 28, 29, 36-39 and 62 stand rejected under 35 U.S.C. § 103(a), for obviousness over Thomas in view of Devi.

Claims 1, 3, 6, 13-15, 19, 30-31, 33 and 36-39 stand rejected under 35 U.S.C. § 103(a), for obviousness over Thomas in view of Fattom.

DISCUSSION

Background

Clostridium difficile, a Gram-positive anaerobic spore-forming bacillus, has been shown to be the etiologic agent of several forms of bacterial induced diarrhea. (Specification 1.)

> A significant component of the pathogenic repertoire of *C. difficile* is found in the two enteric toxins A and B produced by most strains. … Toxin A is primarily an *enterotoxin* with minimal cytotoxic activity. While toxin B is a potent *cytotoxin*, the extensive damage to the intestinal mucosa is attributable to the action of toxin A, however,

> there are reports that toxins A and B may act synergistically in the intestine.

(Specification 2.)

> The repeating units of toxin A, particularly, are immunodominant and are responsible for binding to type 2 core carbohydrate antigens on the surface of the intestinal epithelium (Krivan *et al., Infect. Immun.* 53:573-581 (1986); Tucker, K. and T.D. Wilkins, *Infect. Immun.* 59:73-78 (1991)).

(Specification 2-3.)

> It is further known that
>
> [t]he immunogenicity of the surface polysaccharides of bacterial pathogens is improved when these antigens are bound covalently to a carrier protein (conjugate). Conjugate vaccines against *Haemophillus influenzae* type b have virtually eliminated the disease in developed countries that routinely vaccinate children (Robbins, J.B., and R. Schneerson, *J. Infect. Dis.* 161:821-832 (1990); Robbins *et al., JAMA* 276: 1181-1185 (1996)). This approach to improving the immunogenicity of polysaccharide antigens is based on experiments defining the effect of attaching a hapten (small molecule) or an antigen that is poorly immunogenic by itself to a carrier protein… Conjugates containing polysaccharides from a number of different encapsulated pathogenic microorganisms have been tested in animals and humans and shown to elicit polysaccharide antibodies… Antibodies to surface polysaccharides induced by vaccination with conjugates may confer protection against the encapsulated microorganism by inactivating the innoculum (Robbins *et al. J. Infect. Dis.* 171: 1387-1398 (1995)). Most carriers for conjugate vaccines have been medically useful proteins, namely, inactivated toxins of: tetanus, diphtheria, pertussis and *Pseudomonas aeruginosa.*

(Specification 3.)

Obviousness

Claims 1, 3, 6, 13-15, 19-20, 23-24 and 36-39 stand rejected under 35 U.S.C. § 103(a), for obviousness over Thomas in view of Schneerson.

The Examiner finds that

> Thomas, Jr. et al disclose a composition that contains an antigen, a toxin (*Clostridum difficile, C. novyi, C. sordellii, C. perfringens, C. tetani and C. botulinum*) or a fragment or derivative thereof having adjuvant activity in a pharmaceutically acceptable vehicle (i.e. water, a saline solution, phosphate-buffered saline, a bicarbonate solution or a form of a suppository) (column 1). Thomas, Jr. et al disclose that the *C. difficile* toxins contain the ARU which is the carboxyl-terminal fragment of *C. difficile* toxins A or B having adjuvant activity (column 1). Thomas, Jr. disclose that the toxins of the invention may be covalently coupled or chemically cross-linked to an antigen by standard methods (column 2). Thomas, Jr. et al disclose that intranasal administration of antigens give rise to mucosal immune responses in the upper respiratory tract, gastrointestinal and genito-urinary tracts (column 4). Thomas, Jr. et al disclose that the compositions of the invention can be administered to a patient using standard methods which include oral, rectal, vaginal, intravenous, subcutaneous, intraperitoneal or intramuscular administration (column 3).

(Answer 6.)

Thomas does not teach fusion of *C. difficile* to an antigen of a pathogenic microorganism other than *C. difficile* (*id.*).

The Examiner relies on Schneerson to make up for the deficiencies of Thomas.

> Schneerson et al teach that the serotype 14 *Streptococcus pneumoniae* capsular polysaccharide is poorly immunogenic among the pneumococcal capsular polysaccharides (page 3528). Schneerson et al teach that the development of polysaccharide protein conjugates for prevention of systemic infection caused by *Haemophilus influenzae* type b serves as a precedent for making conjugates of

> polysaccharides of other capsulated pathogens (page 3528). Schneerson teach that conjugation of antigen to improve the immunological properties of other polysaccharides such as *Streptococcus pneumoniae* have been used (page 3528). Schneerson et al teach a conjugate vaccine composed of serotype 14 *Streptococcus pneumoniae* capsular polysaccharide (PN14) bound to Pertussis Toxin. Schneerson et al teach that Pertussis toxin is both a virulence factor and protective antigen of *Bordetella pertussis*. … Schneerson et al further teach that the serotype 14 *Streptococcus pneumoniae*-Pertussis toxin conjugate elicited antibodies in mice to serotype 14 *Streptococcus pneumoniae* at levels estimated to be protective in humans and elicited neutralizing antibodies to Pertussis toxin (see the Abstract).
>
> (Answer 6-7.)
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> The Examiner concludes that
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> [i]t would be prima facie obvious to one of ordinary skill in the art at the time the invention was made to add the serotype 14 *Streptococcus pneumoniae* capsular polysaccharides of Schneerson et al to the immunogenic composition as taught by Thomas, Jr. et al because Schneerson et al demonstrates that serotype 14 *Streptococcus pneumoniae* capsular polysaccharides are poorly immunogenic, but conjugating these capsular polysaccharides to proteins enhances their immunogenicity (3528). It would be expected … that an immunogenic composition comprising the serotype 14 *Streptococcus pneumoniae* capsular polysaccharides of Schneerson et al and the *C. difficile* toxins contain the ARU which is the carboxyl-terminal fragment of *C. difficile* toxins A or B having adjuvant activity of Thomas, Jr. et al would be effective in protecting against a pathogenic microorganism because Schneerson et al teach that covalent attachment of PN14 to protein conferred enhanced immunogencity and T cell dependence (page 3530). Additionally, Thomas, Jr. et al teach that ARU when added to antigen leads to effective mucosal immune responses (column 1).

(Answer 7-8.)

We find no error with the Examiner's reasoning, and agree that the Examiner has provided sufficient evidence to support a prima facie case of obviousness of the claimed subject matter.

Appellants contend there is no motivation to modify or combine the cited references. (Br. 6-7.) In particular, Appellants argue Thomas does not disclose the use of a polysaccharide antigen and does not provide motivation to specifically select a non-*C. difficile* antigen. Appellants also argue Thomas is directed to adjuvant activity of toxin A and there is no specific motivation to select the ARU portion of *C. difficile* from a genus comprising various toxins. (Br. 7-8.)

We are not persuaded by these arguments. If a technique has been used to improve one device, and a person of ordinary skill would recognize that it would be used in similar devices in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1731, 82 USPQ2d 1385, 1396 (2007).

In the present case, Thomas specifically notes that the ARU fragment of *C. difficile* is an effective mucosal adjuvant. (Thomas, col. 6, ll. 63-65.) Thomas created a conjugate between glutathione S-transferase and the ARU portion of toxin A of *C. difficile* and found that the conjugate was shown to be an effective adjuvant when administered intranasally with ovalbumin. (Thomas, col. 12, ll. 56-65.) Thomas further contemplates covalently coupling the toxins to an antigen using standard methods. (Thomas, col. 2, ll. 41-46.) Thus, we agree with the Examiner that there is sufficient motivation in Thomas to combine the ARU portion of toxin A of *C. difficile* with an antigen of a pathogenic organism which is not from *C. difficile*, such as the serotype 14 *Streptococcus pneumoniae* capsular polysaccharides of

Schneerson, for the purpose of inducing an immune response in a mammal and act as an adjuvant (Thomas, col. 1, ll. 39-51). We find a person of ordinary skill would recognize that the ARU fragment of *C. difficile* would be useful in similar fusion proteins in the same way to improve immunogenicity of a weak antigen of a pathogenic microorganism, and that the claimed immunogenic composition is, therefore, obvious in view of Thomas and Schneerson.

The rejection is affirmed.

Obviousness

Claims 1, 3, 6, 13-15, 19-20, 25-26 and 36-39 stand rejected under 35 U.S.C. § 103(a), for obviousness over Thomas in view of Taylor. Claims 1, 3, 6, 13-15, 19-20, 28-29, 36-39 and 62 stand rejected under 35 U.S.C. § 103(a), for obviousness over Thomas in view of Devi. Claims 1, 3, 6, 13-15, 19, 30-31, 33 and 36-39 stand rejected under 35 U.S.C. § 103(a), for obviousness over Thomas in view of Fattom.

Each of Devi, Taylor and Fattom describe linking an antigen from a pathogenic microorganism, such as a bacterial capsular protein, to a toxin molecule to increase its antigenicity and immunogenicity. In particular, Taylor describes linking O-specific polysaccharides of *Shigella dysenteriae* type 1 to recombinant *Pseudomonas aeruginosa* exoprotein A. (Taylor, col. 1, p. 3681.) O-specific polysaccharides are weakly immunogenic alone, however, when the O-specific polysaccharides were linked to *tetanus toxoid*, immunogenicity is increased. (Table 2, p. 3681.) In Fattom, capsular polysaccharides of *S. aureus* were conjugated to *Pseudomonas aeruginosa* Exotoxin A to increase immunogenicity. (Table 4, p. 2371.) In Devi, capsular polysaccharides of *Neisseria meningitis* and

E. coli are known to be poorly immunogenic. (Abstract.) When the capsular polysaccharides were conjugated to tetanus toxoid, they caused an immune reaction that "suggest[ed] that . . . [they would confer] protective immunity." (Abstract.)

We agree with the Examiner that it would have been obvious to one of ordinary skill in the art to substitute the toxin of each of these capsular polysaccharide/protein conjugates with the ARU portion of *C. difficile* with the expectation that such conjugates would also have increased immunogenicity over the capsular polysaccharide alone.

"[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious" the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740, 82 USPQ2d 1385, 1396 (2007). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 127 S. Ct. at 1739, 82 USPQ2d at 1395 (2007). In the present case Appellants combine a portion of *C. difficile* toxin A, ARU, known for its adjuvant function with a weak antigen to yield the predictable result of an increase in the immunogenicity of the antigen. It would further be obvious to one of ordinary skill in the art to combine the ARU with a weak antigen, such as a capsular protein or lipopolysaccharide of bacteria to increase its immunogenicity.

Appellants argue there is no motivation to select ARU from a genus of toxins and combine it with any of the polysaccharides of the cited references. (Br. 8, Reply Br. 4.) We note that the Supreme Court has recently emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the subject matter of the challenged claim, for a court can take account of the inferences and

creative steps that a person of ordinary skill in the art would employ" (*KSR*, 127 S. Ct. at 1741, 82 USPQ2d at 1396).

While Thomas does not specifically suggest that ARU should be combined with each of the specific capsular proteins of the secondary references, Thomas does suggest that one of ordinary skill in the art can use the ARU portion of *C. difficile* toxin A to increase the antigenicity and immunogenicity of an antigen when conjugated to it. From this, one of ordinary skill in the art can infer that the ARU portion of *C. difficile* toxin A can be linked to any weak antigen to increase its immunogenicity with an expectation of success, particularly because the *C. difficile* toxin A is a bacterial toxin, and the secondary references also increase the immunogenicity of a weak antigen by combining it with a bacterial derived toxin molecule.

Similarly, Appellants argue there would have been no expectation of success of achieving the claimed subject matter derived from the cited references and that obvious to try is not the proper obviousness standard. (Br. 10-11.)

However, it is error to conclude that

> a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try.' . . . When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product [is] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR, 127 S. Ct. at 1742, 82 USPQ2d at 1397. For the reasons discussed

herein we find that there would have been an expectation of success on the part of one of ordinary skill in the art to increase the immunogenicity of a weakly immunogenic bacterial capsular protein by combining it with the ARU portion of *C. difficile* Toxin A.

Appellants also argue there is no motivation in Thomas to select an injectable formulation because Thomas leads one to select compositions related to Toxin A of *C. difficile* only formulated for mucosal administration. (Br. 8.) We are not persuaded by this argument. Thomas clearly suggests at col. 3, ll. 13-15, that the adjuvants and antigen may be administered intravenously, subcutaneously and intramuscularly, which are all injectable routes of administration.

In view of the above, the obviousness rejections are affirmed.

CONCLUSION

The rejection of claims 1, 3, 6, 13-15, 19-20, 23-24 and 36-39 under 35 U.S.C. § 103(a), for obviousness over Thomas in view of Schneerson is affirmed The rejection of claims 1, 3, 6, 13-15, 19-20, 25-26 and 36-39 under 35 U.S.C. § 103(a), for obviousness over Thomas in view of Taylor is affirmed. The rejection of claims 1, 3, 6, 13-15, 19-20, 28-29, 36-39 and 62 under 35 U.S.C. § 103(a), for obviousness over Thomas in view of Devi is affirmed. The rejection of claims 1, 3, 6, 13-15, 19, 30-31, 33 and 36-39 under 35 U.S.C. § 103(a), for obviousness over Thomas in view of Fattom is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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